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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/645,706	WOOD ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,9,11,12,15,18,20,21,24-39,41-45,47,60,67,69-71,74,76-78 and 80-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/26/05 has been entered.

Claims 2, 7, 8, 10, 13, 14, 16, 17, 19, 22, 23, 40, 46, 48-59, 61-63, 65, 66, 68, 72, 73, 75, and 79 have been canceled. Claims 1, 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 47, 60, 64, 67, 69-71, 74, 76-78, 80-82 and newly presented claims 83-94 are still at issue and are present for examination.

Claim 64 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 11/18/02.

Applicants' arguments filed on 9/26/05, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 1, 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-83 and 85-94 are rejected under 35

U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (from which claims 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 60, 69, 70 81, 86, 89, and 90 depend), 47 (from which claims 71, 82, and 87 depend), 67 (from which claims 69, 70, 81, and 881 depend), 74 (from which claims 76, 77, 81, and 88 depend), and 78 (from which claims 80, 82, and 87 depend) are vague and indefinite in the recitation of "a reduced number of a combination of mammalian transcription factor binding sequences, intron splice sites, poly(A) addition sites and/or promoter sequences" as without knowing all the possible sequences which are considered to be transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences such a calculation is impossible as one could never obtain a count of the number of such sequence in any reference nucleic acid such that a skilled artisan could determine if the number in the first sequence is reduced relative to the number in the second sequence. While there are clearly art defined specific sequences within each of these categories, each of them is an open-ended group of sequences which includes many unknown members. Clearly while many transcription factors and their associated binding sequences are known in the art, new members

are being added frequently such that the scope of the claims would change. The addition of "wherein the mammalian transcription factor binding sequences are present in a database of transcription factor binding sequences" to claims 1, 47, 67, 74 and 78 and the similar recitation in claim 90 does nothing to clarify what sequences are encompassed without recitation of the specific database and version. Different databases and even different versions of the same database have different sequences included. Claims 91 and 92 (from which claims 93 and 94 depend) are similarly indefinite in the recitation of "known mammalian transcription factor binding sequences"

Applicants argue that the terms "transcription factor binding sequences", "intron splice sites", "poly(A) addition sites" and "promoter sequences" are conventional in the art and argue that these terms are in fact used in the reference cited by the examiner in the 103 rejection. This is acknowledged. However, in the art these terms define a group of sequences related by function. The art does not define clearly **what** sequences are included in the group. Since applicants invention requires a skilled artisan to **quantify** the number of such sequences it is imperative that the artisan know explicitly what sequences are to be included and what sequences are not so one can in fact count them. While the art clearly defines **some**

specific sequences which fall into each group (for example AAUAAA as a polyadenylation sequence) many other sequences may have the same function and not all such sequences are known and taught by the art.

Claim 47 (from which claims 71, 82, and 87 depend) is confusing in the recitation of "hybridizes under medium stringency hybridization conditions to SEQ ID NO:22 (Rluc-final) … and comprises an open reading frame encoding a beetle luciferase" as SEQ ID NO:22 (Rluc-final) is a variant of *Renilla* luciferase which is not a beetle luciferase and in view of the lack of similarity of *Renilla* luciferase with beetle luciferases, a polynucleotide which hybridizes to SEQ ID NO:22 could not encode a beetle luciferase. Claim 83 (from which claim 85 depends) is similarly confusing in the recitation "hybridizes under medium stringency hybridization conditions to SEQ ID NO:22 (Rluc-final) … and comprises an open reading frame encoding a luciferase with 90% amino acid sequence identity to a beetle luciferase".

Claim 90 is confusing in the recitation of "promoter sequences are selected from … AGGA or GGAG if a methionine codon is within 12 bases 3′ of the AGGA or GGAG" as AGGA or GGAG are known in the art to be ribosome binding sequences not promoter sequences.

Claim 93 (upon which claim 94 depends) is indefinite in the recitation of "2-fold fewer mammalian transcription factor binding sequences" as it is unclear if the reference sequence to which the first synthetic nucleic acid molecule is compared is the wild type nucleic acid molecule or the second synthetic nucleic acid molecule.

Claims 1, 3-6, 9, 11, 12, 15, 20-21, 24-33, 35-39, 41-45, 47, 60, 67, 69, 70, 81-83, and 85-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a variant of a parent DNA molecule encoding a reporter polypeptide identical to a reporter polypeptide encoded by said parent DNA, having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized variant of the parent nucleic acid, (2) a variant of a parent DNA molecule encoding a luciferase having 90% identity to the polypeptide encoded by SEQ ID NO:2 and having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized variant of SEQ ID NO:2 or (3) to any nucleic acid which will hybridize to SEQ ID NO:9 under high stringency conditions and

encode a polypeptide having luciferase activity, does not reasonably provide enablement for any variant DNA molecules encoding any reporter polypeptide having at least 90% identity to a wild type reporter polypeptide, having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized version of the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under medium stringency conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 3-6, 9, 11, 12, 15, 20-21, 24-33, 35-39, 41-45, 60, 69, 70, 81, 86, and 89-94 are so broad as to encompass any variant DNA molecules encoding any reporter polypeptide having at least 90% identity to a wild type reporter polypeptide while claims 47, 67, 82, 83, 85, 87, and 88 are so broad as to encompass any variant DNA molecules encoding any luciferase polypeptide having at least 90% identity to any beetle luciferase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant nucleic acids broadly

encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to modifying the nucleic acid sequence of a desired gene without changing the encoded protein sequence.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any variant DNA molecules encoding any reporter polypeptide having at least 90% identity to a wild type reporter polypeptide or any luciferase having at least 90% identity to any beetle luciferase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of any protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any variant DNA molecules encoding any reporter polypeptide having at least 90% identity to a wild type reporter polypeptide or any luciferase having at least 90% identity to any beetle luciferase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variant nucleic acids

having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants first state that it is unclear how medium stringency hybridization conditions are not enabled but high stringency conditions are enabled, as Applicant's specification discloses both. However, the office action does not state that medium stringency conditions are not enabled but that all variant nucleic acids which will hybridize under these conditions are not enabled. Thus it is the scope of nucleic acids encompassed by the conditions that is different from high stringency to medium stringency. The genus of nucleic acids which will hybridize to SEQ ID NO:9 under high stringency conditions is much smaller than that which will hybridize under medium stringency conditions as lower stringency conditions allow nucleic acids with larger numbers of modifications to hybridize.

Next applicants argue that with respect to reporter polypeptides, such as GFP, beetle luciferase, GUS, CAT, and beta-lactamase, applicant has provided evidence that it is well within the skill of the art to introduce substitutions into various reporter proteins and yield a variant protein with the

activity of the corresponding wild-type reporter protein. However, it is noted that the evidence applicants refer to is available for specific GFPs, beetle luciferases, GUS or CAT enzymes, and beta-lactamases but each of these groups of reporter polypeptides includes vast numbers of proteins which are not well characterized and often substantially different from those taught in the art. For example there are many different luminescent beetle species but only a few firefly and click beetle luciferases are well characterized in the art and even these enzymes differ from each other enormously. The rejected claims are not limited the nucleic acids encoding reporters exhibiting high similarity to only those reporters which are well characterized (Note claims that are so limited such as claims 18, 71, 74, 76-78, 80, and 84 are not rejected).

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell transformed with the synthetic nucleic acid, does not reasonably provide enablement for host cells within a multicellular organism that have been transformed with the synthetic nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 44 is so broad as to encompass host cells transformed with specific nucleic acids, including cells in *in vitro* culture as well as cells within any multicellular organism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of genes in a particular host cell and having the desired biological characteristics is

unpredictable the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claims to "An isolated host cell …".

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86 and 89-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Pan et al., Cornelissen et al. (US Patent 5,952,547), and Hey et al. (US Patent 6,169,232).

Sherf et al. teach a modified firefly luciferase gene in which 14% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate restriction sites and sequences which encode transcription factor binding sites for know mammalian transcription factors including ATF, AP1, Sp1, AP2 etc. which would interfere with its genetically neutral behavior expected of a reporter gene. The altered gene includes at least 6 fewer transcription factor binding sites and was inserted into several mammalian expression vectors. The altered gene is transcribed and translated efficiently in mammalian host cells. The altered luciferase differs from the variant nucleic acids of the claims in that 25% or more of the codons were not altered. Sherf et al. further disclose that similar modifications could be made to other luciferase genes including click beetle luciferase

Zolotukhin et al. teach a modified *Aequorea victoria* GFP gene in which 37% of the codons have been altered (and optionally up to even 80-90% may be altered) without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells. The optimized gene is inserted into an expression vector including a Kozak consensus sequence preceding the ATG

initiation codon which optionally may include a multiple cloning site positioned between the promoter and the humanized GFP gene and/or downstream of the GFP gene. The altered gene preferably includes CTG codons encoding leucine, GTG or GTC codons encoding valine, GGC codons encoding glycine, ATC codons encoding isoleucine, CCT codons encoding proline, CGC codons encoding arginine, AGC codons encoding serine, ACC codons encoding threonine, and GGC or GGT codons encoding alanine and is transcribed and translated 5-10 times more efficiently in human cells than the wild type gene.

Donnelly et al. teach a modified hepatitis C virus core antigen gene in which 61% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which encode undesired sequences (such as ATTTA sequences, intron splice sites, etc.) generated by the alteration of the natural codons (see pages 17-18).

Pan et al. teach a modified *Plasmodium falciparum* gene in which a large number of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which might be

detrimental to transcription and translation of the synthetic gene including sequences of promoters, poly A signals, intron splice sites and long runs of purines which might act as transcriptional termination sequences (see pages 1095). It should be noted that the elimination of undesired sequences was performed after the modification of the codon preference and thus would eliminate undesired sequences artificially introduced by the change in codons. The modified gene was successfully expressed in a variety of host cells (see page 1096) while expression of the unmodified gene has turned out to be difficult if not impossible (see page 1095).

Cornelissen et al. teach a modified *Bacillus thuringiensis* gene in which a small number of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to eliminate sequences which might be detrimental to transcription and translation of the synthetic gene and particularly to eliminate sequences of cryptic promoters or DNA regulatory elements thereof which specifically interact with nuclear proteins (i.e., transcription factor binding sequences), see column 5, line 55 - column 6, line 15), and intron splice sites. The modified gene was successfully expressed in transgenic plants.

Hey et al. teach a plant sink protein gene in which a large number of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for plant host cells and eliminate sequences which might be detrimental to transcription and translation of the synthetic gene including sequences of promoters, or elements thereof such as TATA box regions (i.e., a transcription factor binding sequence), poly A signals, intron splice sites, transcriptional termination sequences and runs of 4 or more pyrimidines which might interfere with transcription (see columns 9-12). It should be noted that the elimination of undesired sequences was performed after the modification of the codon preference and thus would eliminate undesired sequences artificially introduced by the change in codons.

Therefore, it would have been obvious to further modify the luciferase gene of Sherf et al. to both increase the codon preference for humans as each of Zolotukhin et al., Donnelly et al., Pan et al. and Hey et al. each teach modifying a large percentage of the codons of a gene to be expressed in a host of interest and to remove potential promoter sequences, transcription binding factor sites, polyadenylation sites and splice sites as each of Sherf et al., Donnelly et al., Pan et

al., Cornelissen et al. and Hey et al. each teach modifying at least several codons of a gene to be expressed in a desired host cell to match the codon preference of the host cell and/or to eliminate undesired sequences in order to increase its expression in the desired host cell and therefore increase its usefulness as a reporter gene in human and other desired host cells. One would have had a reasonable expectation of success in view of the results of the cited references which show that such alterations of other genes substantially improve the levels of expression in a desired host.

Applicants argue with regard to the previous 103 rejection, that the combination of references does not disclose or suggest Applicant's invention as each reference discloses a different wav to modify the coding sequence of a gene to increase expression. This is not persuasive because each of these references is drawn to methods of increasing the expression of a gene in a desired host by altering the sequence of the nucleic acid but not the encoded protein in a variety of ways which will lead to increases in the production of desired protein. The cited references show that the art was clearly aware that a combination of changes in codon preference and removal of sequences detrimental to transcription and/or translation in either the wild type gene or the codon optimized version can be

used to accomplish this goal. While each of the cited references used a different combination of types of modifications, the art clearly teaches all of the claimed modifications encompassed in applicants claims (i.e., mammalian codon optimization, removal of transcription factor binding sequences, removal of splice sites, removal of potential promoters, and removal of polyadenylation sites) and clearly teaches combinations of them with one or more of the others.

Applicants further argue that none of the cited documents recognizes that codon replacement, may create additional transcription factor binding sites, and none of the cited documents removed transcription factor binding sites from a codon optimized gene. While it is true that none of the cited documents explicitly teach that codon replacements may create unwanted transcription factor binding sequences not present in the wild type sequence, Hey et al., Donnelly et al. and Pan et al. all show that the art recognized that codon modifications can **introduce** sequences which are unwanted within the synthetic gene, that additional codon modifications can decrease the introduction of those sequences and Sherf et al. clearly teach that the presence of transcription factor binding sequences within a reporter gene is an unwanted feature as it may interfere with the desired genetic neutrality of the reporter

gene (see column 8). Furthermore, it is obvious on its face that anytime a gene sequence is altered that one necessarily creates new sequences which were not previously present and that merely by random chance some of these newly created sequences may be detrimental. It is even further obvious on its face that the more changes one makes, the higher the chances that such a detrimental sequence will be introduced. Sherf et al. made only limited changes to codon selection and thus at least in his explicit teachings focused on the elimination of detrimental sequences present in the wild type sequence. However, the remaining art clearly would have motivated one of skill in the art to make more substantial changes in codon preference within the luciferase of Sherf et al. Furthermore the disclosures of Hey et al., Donnelly et al. and Pan et al. would have clearly led a skilled artisan to scan not only the wild type sequence for the unwanted transcription factor binding sites but also the codon optimized version thereof.

Applicants argue that if altering codon composition in an open reading frame to codons preferred in a heterologous host alone increases expression in the heterologous host, then there would be no motivation for the art worker to make any other changes, e.g., those which may reduce aberrant transcription. And that the cited art does not point to which changes in

combination, i.e., a combination of transcription factor binding sites, and intron splice sites, poly(A) sites and/or promoter sequences would be useful in that regard. This is not persuasive because merely because one has made a useful improvement in something does not stop a skilled artisan from seeking additional improvements also. The art clearly teaches several distinct methods of increasing expression of a gene in a heterologous host which a skilled artisan would clearly be motivated to combine with the expectation that the combination would be superior to any of the methods alone. Furthermore, applicants argument that the cited art does not point to which combination of methods would be useful is not persuasive as applicants claims are not drawn to any combination in particular (note all applicants claims recite a combination of transcription factor binding sites, intron splice sites, poly(A) sites and/or promoter sequences such that any combination of one or more of these is included) and the art clearly teaches several combinations of these.

Applicants finally argue that one of ordinary skill in the art in possession of the cited art would have no reasonable expectation that any particular set of changes would improve activity in a gene that is to be expressed in a highly evolutionarily distinct cell. This is not persuasive because

the art clearly provide an expectation that codon optimization and the elimination of a variety of types of sequences which are detrimental to transcription and/or translation will improve the expression of a gene in a heterologous host. While it is acknowledged that one cannot be certain that the modifications will not have unexpected consequences, applicants are reminded that obviousness does not require an absolute certainty of success but only a reasonable expectation thereof.

Claims 47, 71, 74, 76-78, 80, 82-85, 87, and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Pan et al., Cornelissen et al. (US Patent 5,952,547), and Hey et al. (US Patent 6,169,232) as applied to claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86 and 89-94 above, and further in of Wood et al. (WO 99/14336).

Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al. are discussed above. Sherf et al. teach that additional genes encoding luciferase can be similarly optimized for human expression. Wood et al. teach a gene encoding a yellow green click beetle luciferase gene 97% identical to SEQ ID NO:2 herein. Therefore, it would have been obvious to one of skill in the art to optimize the expression of

the yellow-green click beetle luciferase gene of Wood et al. in human cells as taught by the combined disclosures of Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 and 58-60 of copending Application No. 10/314,827.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 herein and claims 1-50 and 58-60 of copending Application No. 10/314,827 are all directed to synthetic nucleic acids encoding a reporter polypeptide in which more than 25% of the codons have been replaced with mammalian high usage codons or codons selected to reduce the number of transcription factor binding sequences present in a wild-type sequence or introduced by the codon optimization. The claims differ in a variety of individual features such as the type of reporter polypeptide produced, the variety of sites present in the wild type nucleic acid or the codon optimized variant thereof which are eliminated, and the number of alterations of the sequence of the wild-type reporter polypeptide which may be introduced into the polypeptide encoded by the synthetic nucleic acid. However the preferred embodiments of the synthetic nucleic acid molecules of the copending application (i.e., those recited in claim 36 of the copending application) would clearly anticipate claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 herein. Claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 herein cannot be considered patentably distinct over claims 1-50 and 58-60 of copending Application No. 10/314,827 when there is a

specifically recited embodiment that would anticipate the instant claims. Alternatively, claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 herein cannot be considered patentably distinct over claims 1-50 and 58-60 of copending Application No. 10/314,827 when there is a specifically disclosed embodiment in the copending application that supports claims 1-50 and 58-60 of copending Application No. 10/314,827 and falls within the scope of claims 1, 3-6, 15, 20, 21, 24-39, 41-45, 60, 81, 86, and 89-94 herein because it would have been obvious to one having ordinary skill in the art to select the preferred embodiments of synthetic nucleic acids that support the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652

Continuation of Disposition of Claims: Claims pending in the application are 1,3-6,9,11,12,15,18,20,21,24-39,41-45,47,60,64,67,69-71,74,76-78 and 80-94.